

REMARKS

Claims 1, 6-32, 58-65, 70-90, 95-104 and 135-153 are pending. Claims 1, 6-16, 65, 70-90, 95-104, 138, 139, 141 and 144-153 are under examination. Claims 81-89 have been canceled without prejudice to Applicants pursuing these claims in a related application.

Rejections Under 35 U.S.C. § 112, First Paragraph

The rejection of claims 1, 6-16, 65, 70-90, 95-104, 138, 139, 141 and 144-153 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement is respectfully traversed. Applicants respectfully maintain that the specification provides sufficient description and guidance to enable the claimed methods.

The claims are directed to methods of determining a comparative expression profile and diagnosing a health state. The method can include the steps of determining a multidimensional coordinate point representative of the expression levels of a sample of molecules in a population of molecules in a specimen from the individual; comparing the multidimensional coordinate point to a health-associated reference expression region of the sample of molecules; and determining if the multidimensional coordinate point is within or outside the health-associated reference expression region, wherein the multidimensional coordinate point within the health-associated reference expression region indicates a reference expression profile and wherein the multidimensional coordinate point outside the health-associated reference expression region indicates a perturbed expression profile. The method can also include determining the expression levels of a sample of molecules in a population of molecules in a specimen from an individual; comparing the expression levels with a health-associated reference expression region of the sample of molecules; and determining if the expression levels of the sample of molecules is within or outside the health-associated reference expression region, wherein expression levels within the health-associated reference expression region indicates a reference health state and wherein expression levels outside the health-associated reference expression region indicates a disease state or a perturbed health state.

Applicants maintain, for the reasons of record, that the claimed methods are sufficiently enabled by the teachings in the specification. The specification teaches a variety of methods

enabling one skilled in the art to make and use the invention as claimed. In particular, the specification teaches that the methods of the invention can be used to diagnose the health state or disease state of an individual using the expression levels of molecules (page 11, lines 16-29). An individual having expression levels of molecules that fall within a health-associated reference expression region indicates a reference expression profile. An individual having molecules with expression levels outside the health-associated reference expression region indicates a perturbed health state, which can be a disease state. The specification also teaches that methods of the invention use a statistically determined health-associated reference expression region of molecules indicative of expression levels of molecules in a population of molecules having a selected health state (page 12, line 19, to page 13, line 8). The expression levels of molecules in a specimen from an individual can be compared to the statistically determined health-associated reference expression region to determine a comparative expression profile of the individual relative to the reference population. The determination of the reference expression region of a variety of molecules provides a basis for comparing any individual to determine if the individual has one or more molecules with aberrant expression or molecules having aberrant relative expression. Thus, the determination of a health-associated reference expression region for any number of molecules expressed in a cell provides a central repository of information, which can be accessed by a variety of means to determine a comparative expression profile of an individual.

The specification also teaches various statistical methods for determining the health state of an individual (page 12, line 19, to page 13, line 13; page 19, line 29, to page 21, line 29; page 23, line 13, to page 25, line 17; and page 39, line 22, to page 44, line 26). The specification additionally teaches methods for selecting a reference population and a sample of molecules predictive of the health state of an individual (page 70, line 1, to page 79, line 6). The specification further teaches that it is not necessary to know or determine the identity of the molecules for which the expression levels are determined, only that a specimen molecule has a measurable expression level correlated with the health state of the individual (page 44, line 27, to page 45, line 7). Accordingly, Applicants respectfully maintain that the specification provides sufficient description and guidance to enable the claimed methods and, therefore, request that this rejection be withdrawn.

Rejections Under 35 U.S.C. § 112, Second Paragraph

The rejection of claims 1, 6-16, 65, 70-90, 95-104, 138, 139, 141 and 144-153 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite is respectfully traversed. Applicants respectfully maintain that the claims are clear and definite.

Applicants maintain, for the reasons of record, that the terms “determining” and “comparing” are clear and definite. As discussed in the previous response, the specification teaches various methods for determining and comparing expression levels of a multidimensional coordinate point. Furthermore, it is respectfully submitted that one skilled in the art would readily understand the meaning of “determining” and “comparing.” The claimed methods use statistical analysis to determine whether a value lies within or outside a reference expression region. It is respectfully maintained that one skilled in the art would readily understand how to determine values and compare the values to a reference expression region based on the teachings in the specification and what was well known in the art. Therefore, it is respectfully submitted that the scope of the claim is clear to one skilled in the art. Accordingly, Applicants respectfully maintain that these claims are clear and definite and request that this rejection be withdrawn.

Rejections Under 35 U.S.C. § 102

The rejection of claims 1, 6-16, 65, 70-90, 95-104, 138, 139, 141 and 144-153 under 35 U.S.C. § 102(e) as allegedly anticipated by Friend et al., U.S. Patent No. 6,324,479 (hereinafter Friend et al. ‘479), is respectfully traversed.

Applicants submit that Friend et al. ‘479 does not teach the claimed methods. In particular, Friend et al. ‘479 does not teach the claimed methods of determining a comparative expression profile or diagnosing a health state. Friend et al. ‘479 describes unidimensional analysis, in contrast to the claimed methods using multidimensional analysis. In corroboration of Applicants’ position that Friend et al. ‘479 does not teach the claimed methods, attached is a Rule 132 Declaration (Exhibit 1) signed by the inventors, Dr. Hood and Dr. Siegel. In the Declaration, Drs. Hood and Siegel attest that the claimed methods are distinct from Friend et al. ‘479. The Declaration discusses the differences between the claimed methods and the methods described by Friend et al. ‘479, and these differences are exemplified in Exhibits A and B

attached to the Declaration. It is respectfully submitted that the Declaration by Drs. Hood and Siegel corroborate Applicants' position that Friend et al. '479 does not teach the claimed methods.

With regard to leukocyte specimens, Applicants respectfully disagree with the assertion in the Office Action on page 3 that Friend et al. '479 discloses the use of white blood cells and is a disclosure of the use of leukocytes, referring to "T cells" in column 23. In column 23, the only reference to "T cells" is in the paragraph on lines 20-40, in which there is a description of T cell receptor activation of tyrosine kinases. There is no description of the use of T cells, white blood cells or leukocytes in Friend et al. '479, let alone the use of leukocytes as a specimen to determine the expression levels of molecules, as recited in claims 9, 25, 64, 73, 97 and 144.

Applicants submit that Friend et al. '479 does not teach Applicants' claimed methods, as discussed above and corroborated by the attached Declaration signed by Drs. Hood and Siegel (Exhibit 1). Absent such a teaching, Friend et al. '479 cannot anticipate the claims. Accordingly, Applicants respectfully request that this rejection be withdrawn.

The rejection of claims 1, 6-16, 65, 70-90, 95-104, 138, 139, 141 and 144-153 under 35 U.S.C. § 102(e) as allegedly anticipated by Friend et al., publication US 2001/0018182 (hereinafter Friend et al. '182), is respectfully traversed.

Applicants submit that Friend et al. '182 does not teach the claimed methods. In particular, Friend et al. '182 does not teach the claimed methods of determining a comparative expression profile or diagnosing a health state. Friend et al. '182 describes unidimensional analysis, in contrast to the claimed methods using multidimensional analysis. In corroboration of Applicants' position that Friend et al. '182 does not teach the claimed methods, attached is a Rule 132 Declaration (Exhibit 1) signed by the inventors, Dr. Hood and Dr. Siegel. In the Declaration, Drs. Hood and Siegel attest that the claimed methods are distinct from Friend et al. '182. The Declaration discusses the differences between the claimed methods and the methods described by Friend et al. '182, and these differences are exemplified in Exhibits A and B attached to the Declaration. It is respectfully submitted that the Declaration by Drs. Hood and Siegel corroborate Applicants' position that Friend et al. '182 does not teach the claimed methods.

With regard to leukocyte specimens, Applicants respectfully disagree with the assertion in the Office Action on page 4 that Friend et al. '182 discloses the use of leukemia and is a disclosure of leukocytes, referring to Table 1. Table 1 on page 4 of Friend et al. '182 lists "Malignancies and Related Disorders" and is described as providing a list of "[E]xemplary types of cancer." A description of leukemia as an exemplary form of cancer in no way teaches the use of leukocytes as a specimen to determine the expression levels of molecules, as recited in claims 9, 25, 64, 73, 97 and 144.

Applicants submit that Friend et al. '182 does not teach Applicants' claimed methods, as discussed above and corroborated by the attached Declaration signed by Drs. Hood and Siegel (Exhibit 1). Absent such a teaching, Friend et al. '182 cannot anticipate the claims. Accordingly, Applicants respectfully request that this rejection be withdrawn.

In light of the amendments and remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. The Examiner is invited to call the undersigned agent if there are any questions.

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To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

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A handwritten signature in black ink, appearing to read "Deborah L. Cadena".

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